Outcomes for Women in Phase 3 Trials of Long-Acting Cabotegravir + Rilpivirine: Pooled ATLAS and FLAIR Week 48 Results

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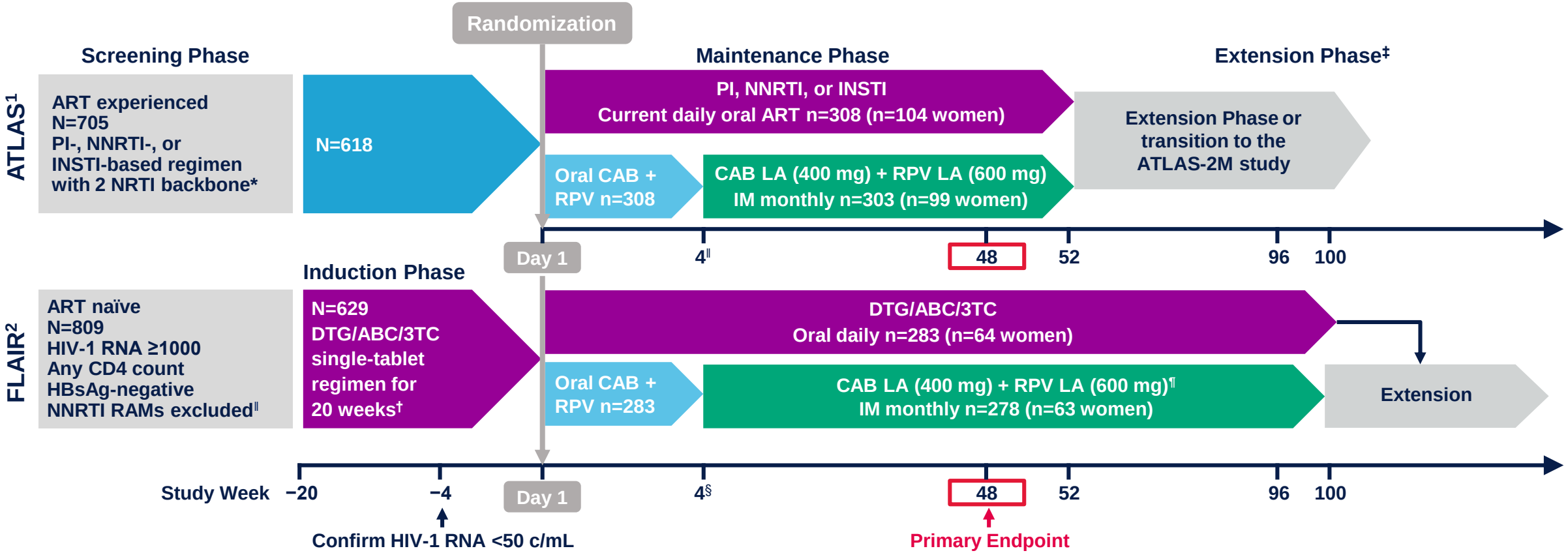
ATLAS and FLAIR: Background and Objectives

- The mainstay of HIV treatment remains once-daily oral regimens
  - However, despite the success of daily oral therapy, considerable interest exists in long-acting (LA) options
- Cabotegravir (CAB) and rilpivirine (RPV) injectable formulations are under development as a novel two-drug LA therapeutic regimen for the maintenance of HIV virologic suppression
- ATLAS* and FLAIR† are two randomized, open-label, international Phase 3 studies that demonstrated non-inferiority of switching to monthly intramuscular (IM) injections of CAB + RPV LA vs current antiretroviral regimen (CAR)[1,2]
- Globally, there are more women living with HIV than men,[3] yet women are often under-represented in HIV clinical trials
- The present analysis thus aimed to examine the safety, efficacy, patient satisfaction, and retention of women across the ATLAS and FLAIR studies

1. Swindells S, *et al.* CROI 2019; Seattle, WA. Abstract 1475; 2. Orkin C, *et al.* CROI 2019; Seattle, WA. Abstract 3947;
3. WHO. Summary of the global HIV epidemic (2018). Available at: https://www.who.int/hiv/data/2018_summary-global-hiv-epi.png?ua=1. Last accessed October 3, 2019. *NCT02951052. †NCT02938520.

ATLAS and FLAIR Study Design

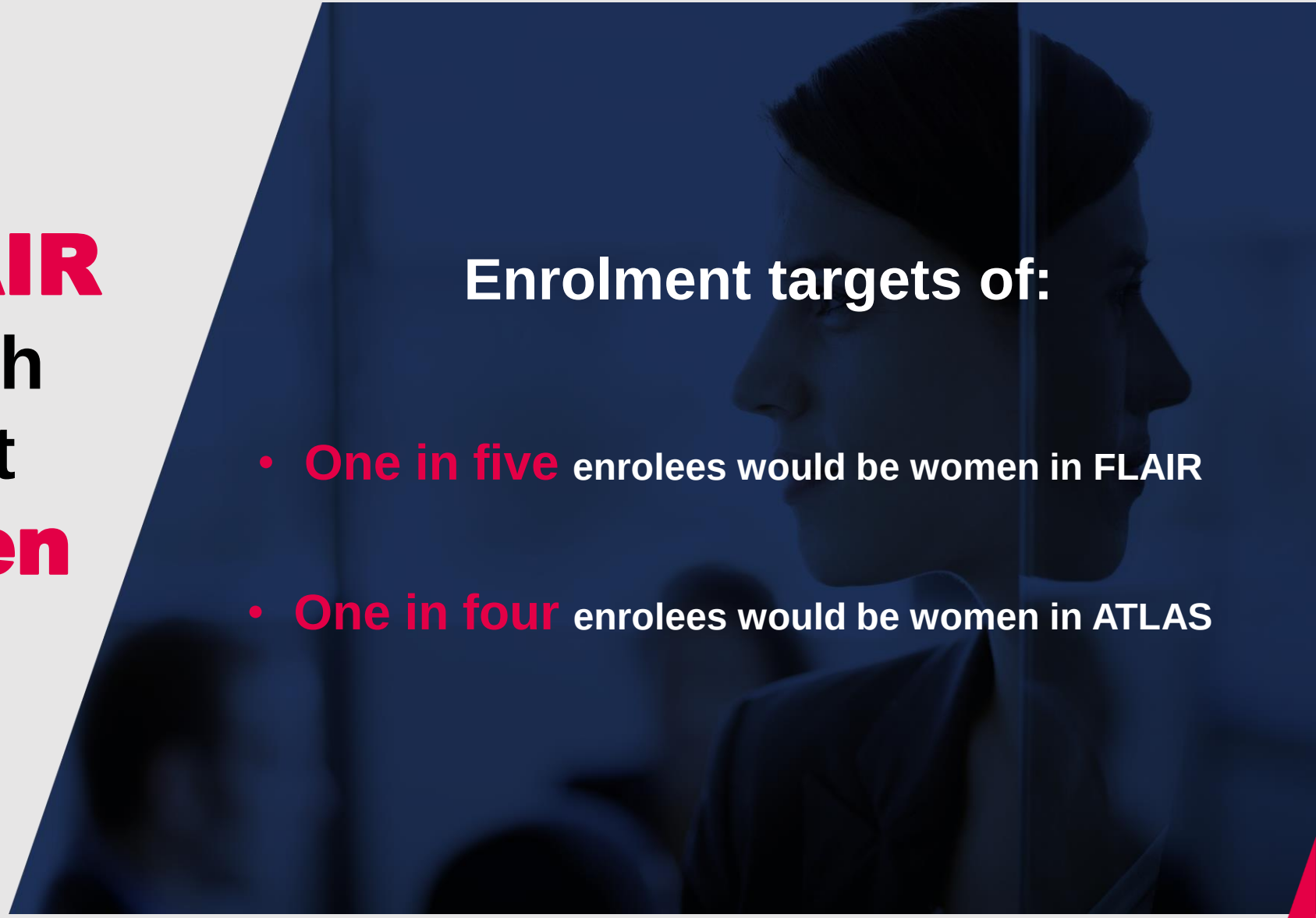
Randomized, Multicenter, International, Open-Label, Non-Inferiority Studies



*Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; Triumeq excluded from study. †DTG plus 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive (n=30 as last regimen during induction: n=2 discontinued during induction, n=14 randomized to CAB LA + RPV LA, n=14 randomized to DTG/ABC/3TC arm and continued on DTG plus 2 alternative non-ABC NRTIs in Maintenance Phase). ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR. §Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks. ‖NNRTI RAMs but not K103N were exclusionary. ¶Participants who withdraw/complete CAB LA + RPV LA enter 52-week long-term follow-up.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; DTG, dolutegravir; IM, intramuscular; INSTI, integrase strand transfer inhibitor; HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; VL, viral load.

1. Swindells S, *et al.* CROI 2019; Seattle, WA. Abstract 139; 2. Orkin C, *et al.* CROI 2019; Seattle, WA. Abstract 140.

ATLAS and **FLAIR** were designed with specific enrolment targets for **women**



Enrolment targets of:

- **One in five** enrolees would be women in FLAIR
- **One in four** enrolees would be women in ATLAS

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ATLAS and FLAIR Methods and Subgroup Analysis

- Injections were scheduled every 4 weeks with a ± 7-day dosing window* of the projected dosing date†
- Pooled analysis was performed based on:
  - HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot; primary endpoint)
  - HIV-1 RNA <50 c/mL at Week 48
  - Safety assessments
  - Treatment satisfaction (HIV-Treatment Satisfaction Questionnaire)
- Subgroup analyses by sex at birth was pre-planned

*Dosing window: –7 days for the second and third injections, and ±7 days thereafter. †Projected dosing date is relative to date of first injection at Week 4b.

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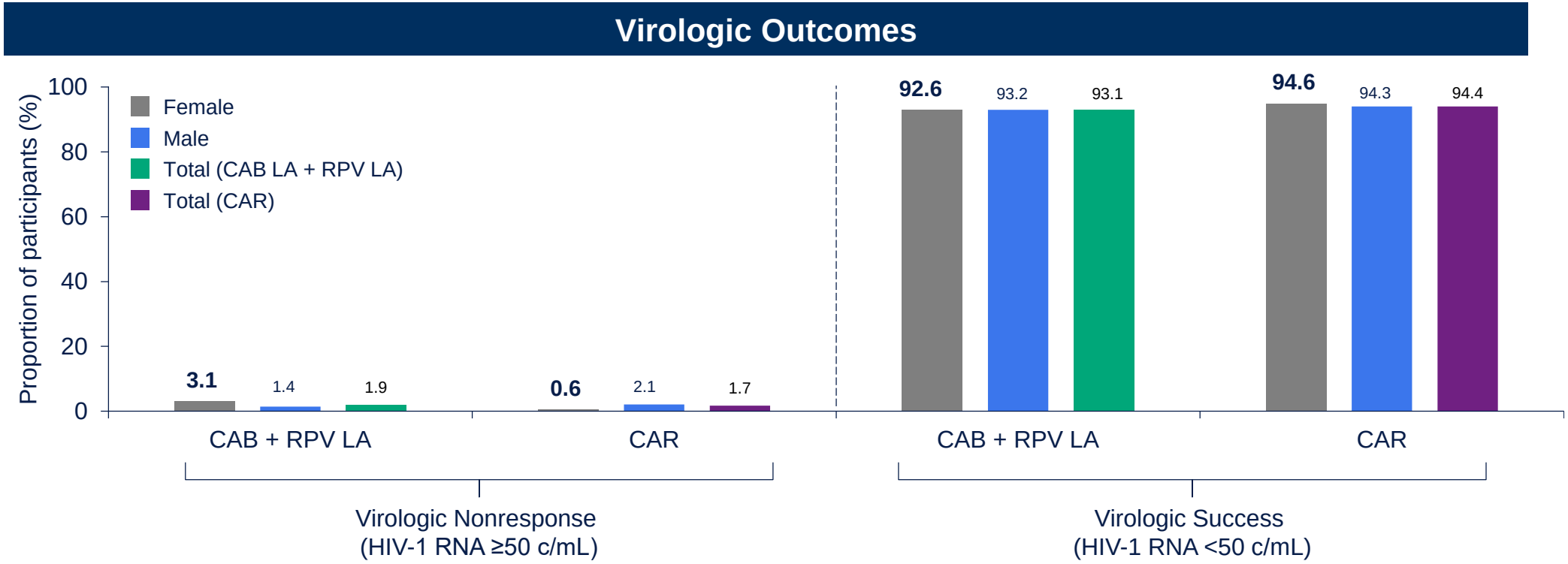
ATLAS and FLAIR: Baseline Characteristics*

- 27% and 28% women were randomized to LA and CAR arms, respectively

	CAB LA + RPV LA N (%)		CAR N (%)	
	Women	Men	Women	Men
Sex at birth	162 (27)	429 (73)	168 (28)	423 (72)
Age (mean in years)	41	38	43	38
BMI ≥30 (kg/m²)	44 (27)	56 (13)	48 (29)	55 (13)
Race:				
Black or African American	59 (36)	50 (12)	69 (41)	64 (15)
White	92 (57)	338 (79)	93 (55)	315 (74)
Asian	8 (5)	26 (6)	3 (2)	25 (6)
Other	3 (2)	15 (3)	3 (2)	17 (4)
Region†:				
Europe and North America	75 (46)	316 (74)	83 (49)	322 (76)
Russian Federation	44 (27)	57 (13)	45 (27)	53 (13)
South Africa	34 (21)	15 (4)	36 (21)	18 (4)

*The baseline demographics have been previously described (Overton E, *et al*. IAS 2019. Poster MOPEB257). †The three regions with the highest enrollment and randomization of women.
BMI, body mass index; CAB, cabotegravir; CAR, current antiretroviral; LA, long-acting; RPV, rilpivirine.

High Rates of Virologic Success was Observed in both Women and Men in ATLAS and FLAIR



At Week 48, virologic non-response was infrequent, with 92.6% of women having virologic success with the LA regimen

CAB, cabotegravir; CAR, current antiretroviral; LA, long-acting; RPV, rilpivirine.

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ATLAS and FLAIR Confirmed Virologic Failure* in Women: CAB LA + RPV LA Arm

Country, HIV-1 Subtype	Study	SVF Timepoint	Viral Load at SVF/CVF (c/mL)	BMI >30 kg/m²	Baseline RAMs (PBMC/HIV-1 DNA; Day 1)		SVF Timepoint RAMs (HIV-1 RNA)		Drug Sensitivity at SVF§ (Fold Change)		
					RT	INSTI‡	RT	INSTI‡			
Russia, A/A1	ATLAS	Week 8	79,166 / 25,745	No	E138E/A	None	E138A	None	**RPV (2.4)**	CAB (0.8)	DTG (0.9)
France, AG	ATLAS	Week 12	695 / 258	Yes	V108V/I E138K	None	V108I E138K	None	**RPV (3.7)**	CAB (1.2)	DTG (1.0)
Russia, A1	FLAIR	Week 20	373 / 456	Yes	None	None	E138E/A/ K/T	Q148R	**RPV (7.1)**	**CAB (5.2)**	DTG (1.0)
Russia, A1	FLAIR	Week 48	488 / 440	Yes	None	None	E138K	Q148R	RPV (1.0)	**CAB (9.4)**	DTG (1.1)

- Seven (1.2%, LA; and 1.2%, CAR) confirmed virologic failures (CVFs) occurred in each arm, with 5/7† (LA) and 2/7 (CAR) arising in women
- Plasma CAB and RPV concentrations for women at the time of failure were below the population means but within the range for the large majority of individuals who maintained virologic suppression

*Where CVF is defined as rebound as indicated by two consecutive plasma HIV-1-RNA levels ≥200 c/mL after prior suppression to <200 c/mL. †One participant in FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected VF that was confirmed. ‡L74I is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity. §Monogram biological/clinical cutoffs are: RPV=2.0, CAB=2.5, and DTG=4.0.

BMI, body mass index; CAB, cabotegravir; CAR, current antiretroviral; CVF, confirmed virologic failure; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; PBMC, peripheral blood mononuclear cell; RAM, resistance-associated mutation; RPV, rilpivirine; RT, reverse transcriptase; SVF, suspected virologic failure; VF, virologic failure.

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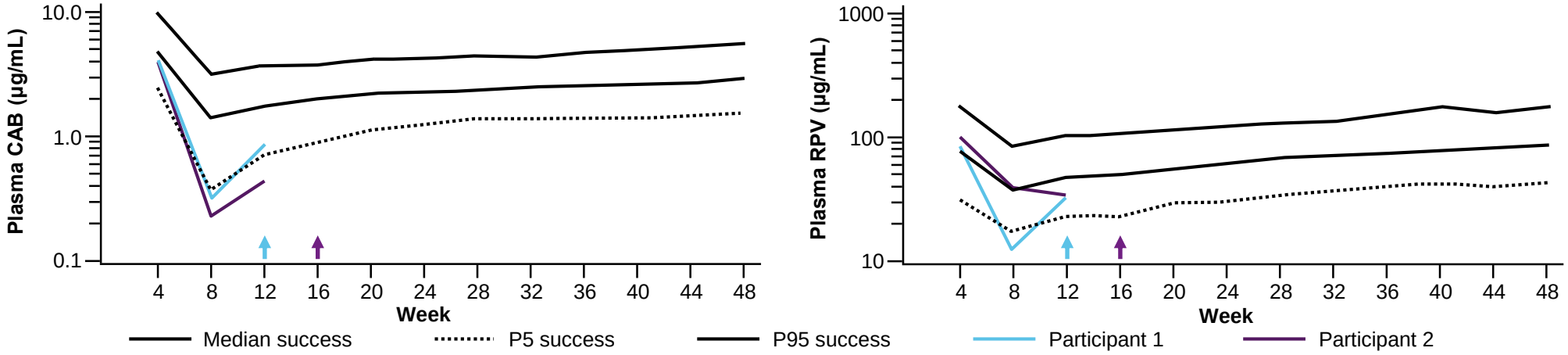
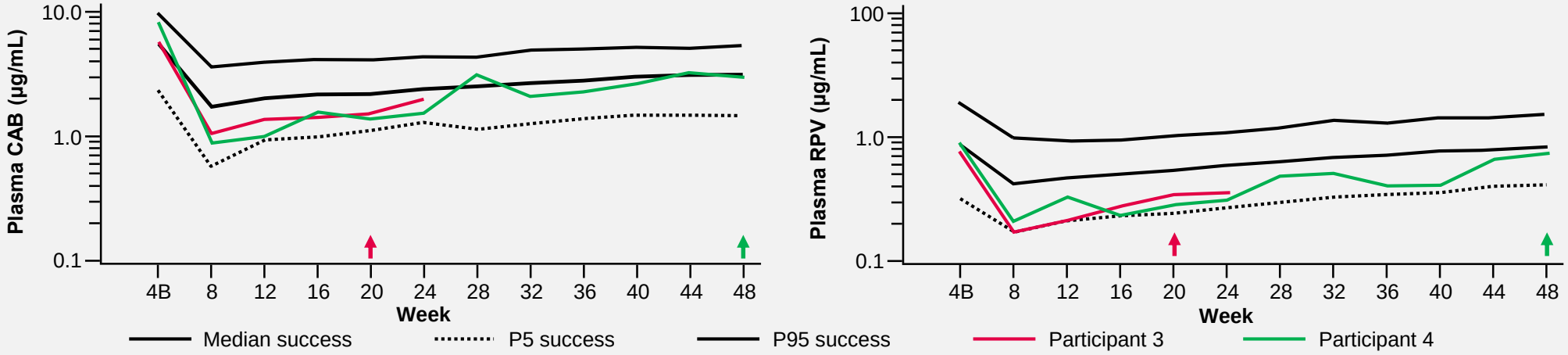
ATLAS and FLAIR: Individual Concentration-Time Profiles for CAB and RPV CVFs Compared with Median Profiles for Successes

In ATLAS and FLAIR, CAB and RPV concentration-time profiles for women with CVF were within the range of exposures that show efficacy in most participants, indicating that other factors may have contributed to failure

ATLAS



FLAIR



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Reported Adverse Events Rates in Women Were Similar to Those Observed in Men

Summary of pooled ATLAS and FLAIR data by sex at birth over 48 weeks						
Event*	**CAB + RPV LA n (%)**			**CAR n (%)**		
	Women (n=162)	**Men (n=429)**	**Total (N=591)**	**Women (n=168)**	**Men (n=423)**	**Total (N=591)**
Any AE†	148 (91.0)	413 (96.0)	561 (95.0)	122 (73.0)	323 (76.0)	445 (75.0)
Grade 3–5 AE	10 (6.0)	56 (13.0)	66 (11.0)	9 (5.0)	26 (6.0)	35 (6.0)
Drug-related AE†	126 (78.0)	365 (85.1)	491 (83.1)	6 (4.0)	30 (7.1)	36 (6.1)
Severe AEs	6 (3.7)	25 (5.8)	31 (5.2)	9 (5.4)	17 (4.0)	26 (4.4)
Drug-related SAE	0	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	1 (<1.0)
AE leading to withdrawal‡	4 (2.0)	18 (4.2)	22 (3.7)	4 (2.4)	5 (1.2)	9 (1.5)

Overall AE profiles are similar between women and men

No cases of drug hypersensitivity or drug-induced liver injury were observed

No drug-related SAEs or deaths occurred in women§

*Data are number and percentages of participants with at least 1 of the respective AEs through Week 48. †High proportion of AEs in the CAB LA + RPV LA arm associated with ISRs. ‡Events leading to withdrawal included: CAB LA + RPV LA arm: acute hepatitis A (1), hepatitis B (2), hepatitis C (1), acute hepatitis A/secondary syphilis (1), injection site pain (1), injection site pain/general discomfort/diarrhea/vomiting (1), increased transaminases (1), and adenocarcinoma of colon (1); CAR arm: fatigue/nausea/dizziness (1), amnesia/disturbance in attention/dysarthria (1), suicide attempt (1), and renal failure (1). §One death was reported in a women in the CAR arm of ATLAS but this was not considered treatment related (methamphetamine overdose).
AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine. SAE, serious AE.

ATLAS and FLAIR Injection Site Reactions

Event	CAB LA + RPV LA: Women N=162	CAB LA + RPV LA: Men N=429
Participants receiving injections, n (%)	159 (98)	422 (98)
Injections given, n	3958	10,724
Participants with ISR events, n (%)	128 (81)	361 (86)
Pain	107 (66)	351 (82)
Nodule	25 (15)	56 (13)
Induration	32 (20)	36 (8)
Swelling	15 (9)	31 (7)
Grade 3-5 ISR pain*	1 (<1)	21 (5)
Grade 3 ISR pain	1 (<1)	21 (5)
Median duration of ISRs, days	3	3
Participants with ISR leading to withdrawal, n (%)	2 (1)	4 (<1)

- The number of ISR events was comparable between women and men
- *There were no Grade 4 or 5 ISRs in women or men

CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

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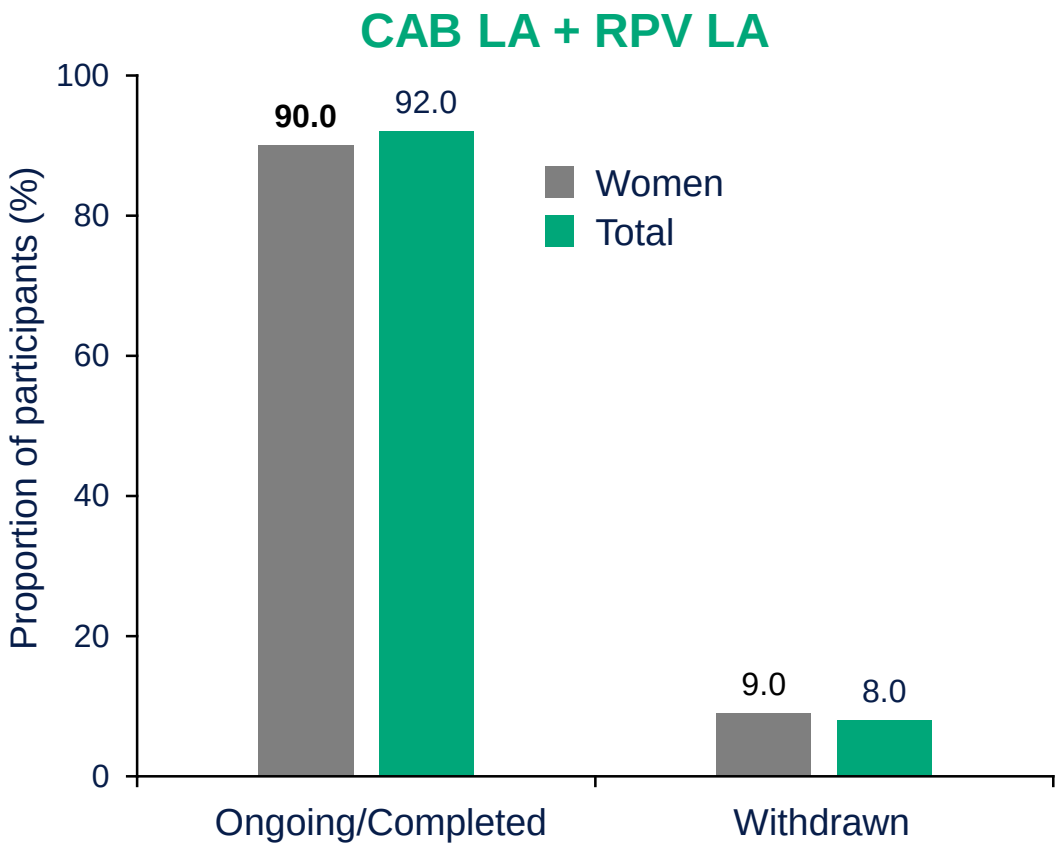
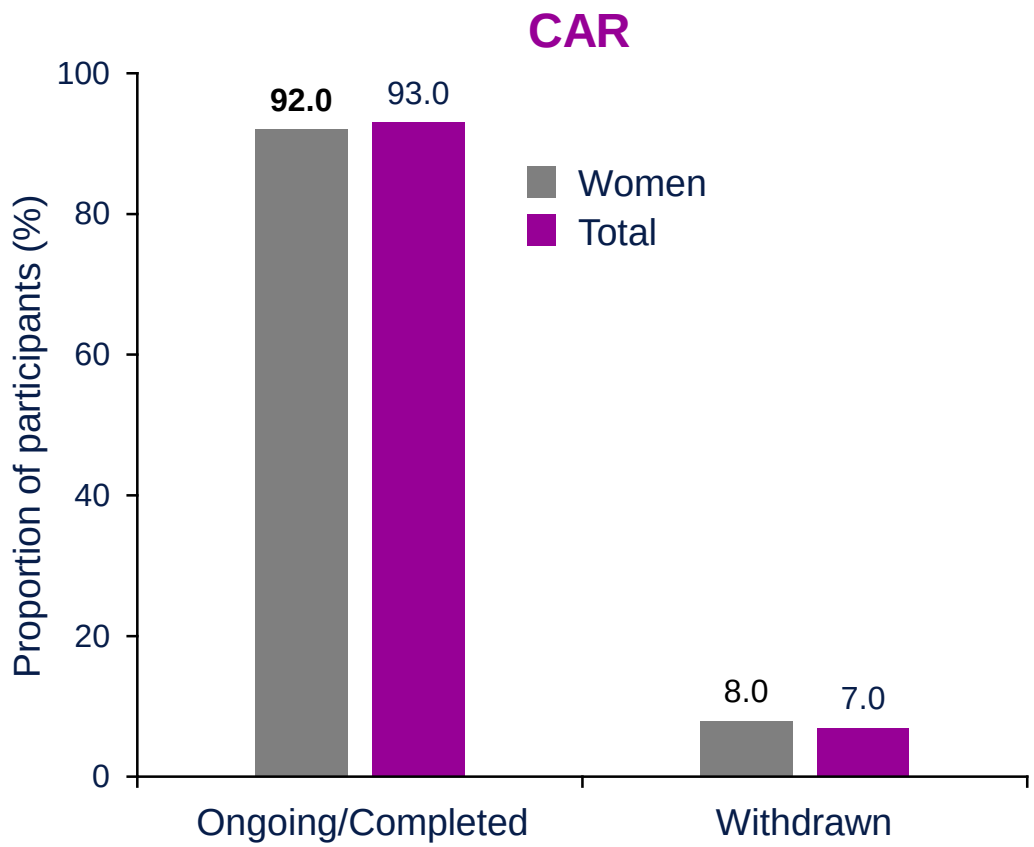
The Majority of Women Retained in the ATLAS and FLAIR Studies at Week 48





For women, n=93, 54 and 15 for CAB + RPV at Week 48 were, ongoing, completed, or withdrawn, respectively; n=59, 95, and 14 for CAR at Week 48 were ongoing, completed, or withdrawn. For total, n=368, 176, and 47 for CAB + RPV at Week 48 were ongoing, completed, or withdrawn, respectively; n=266, 286, and 39 for CAR at Week 48 were ongoing, completed, or withdrawn.
CAB, cabotegravir; CAR, current antiretroviral; LA, long-acting; RPV, rilpivirine.

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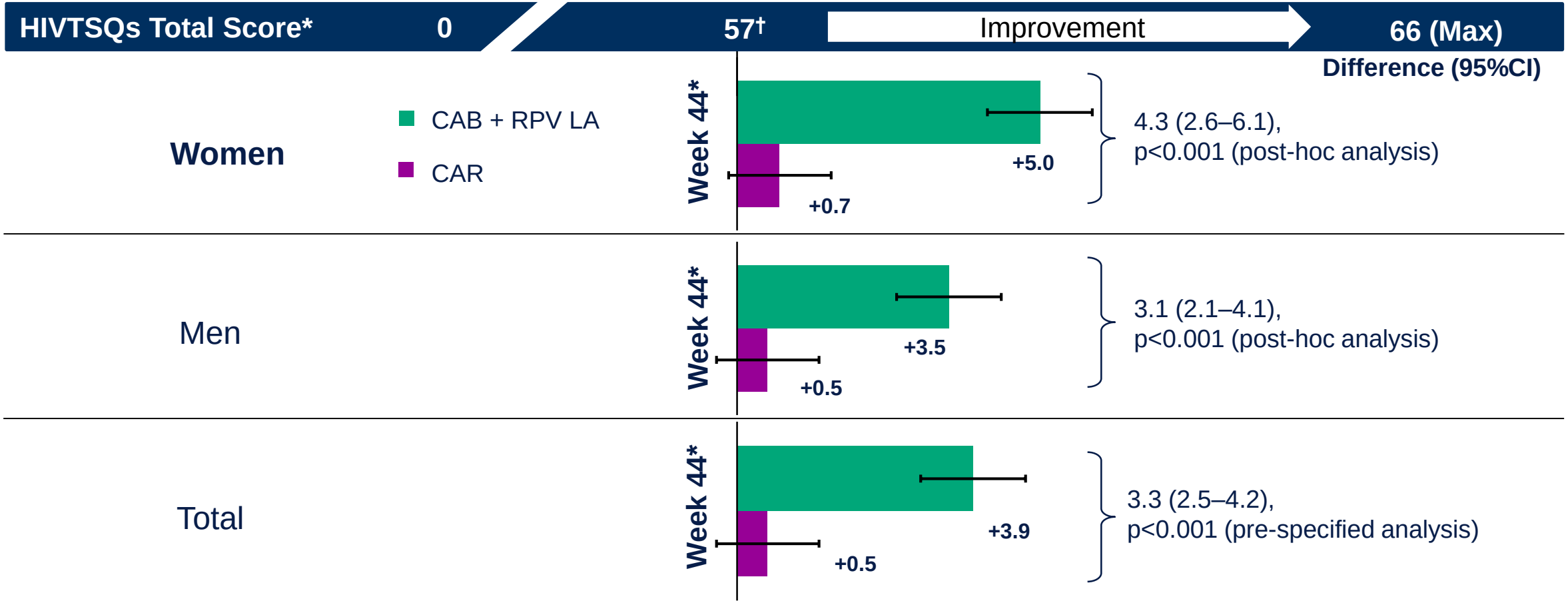
CAB + RPV LA Participants Showed Higher Treatment Satisfaction (HIVTSQ) compared with CAR Participants at Week 44 (Pooled Data)



*Adjusted mean change from baseline; adjusted for baseline score, sex, age, race, and baseline third agent class. Error bars show 95% CI. †Baseline HIVTSQs scores were 57.7 (n=151), 56.9 (n=406), and 57.1 (n=557) for CAB + RPV LA participants (women, men, and total), and 56.2 (n=155), 57.5 (n=395), and 57.1 (n=550) (women, men, and total) for CAR participants.
CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; HIVTSQs, HIV Treatment Satisfaction Questionnaire (Status); LA, long-acting; RPV, rilpivirine.

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ATLAS and FLAIR: Conclusions

- Monthly CAB LA + RPV LA was non-inferior to daily oral three-drug regimens and demonstrated high efficacy in women
- Virologic failure was low for both women and men
- Women had lower rates of AEs compared to men, and treatment discontinuations were low and comparable in both groups
- Retention rates and treatment satisfaction with LA were high in both studies
- These results support the therapeutic potential of once-monthly CAB LA + RPV LA for women

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